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EXAMINER
BERCH, MARK L

ART UNIT	PAPER NUMBER
1624	

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/859,503	MCKENNON ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 18-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. There still remains original point 3. Sulfonyl is a divalent group. It is depicted as such in the CRC reference which applicants provided, and page 31, line 19 explicitly says that it is a divalent group. The remarks says that it is "defined on page 31 ... as representing $-SO_2$ such as alkyl—SO_2-." That is <u>not</u> what the specification says. It says that sulfonyl can be "linked to other terms such as alkylsulfonyl". However, when it is not so linked, it is a divalent group as the specification states. Further, while applicants state that references to sulfinyl have been removed, this is not so. Applicants then go on to argue this point, but this is not persuasive either. Applicants point to e.g. page 14, line 6, but that is not the sulfinyl radical, which is -SO-, but instead the -S(O)-alkyl radical, which is monovalent and is a <u>different</u> radical. The CRC reference clearly depicts sulfinyl as divalent. Applicants cannot use a divalent choice for a monovalent radical.

2. There still remains original point 7. Applicants cite the Hawley's dictionary as indicating that "thio" is a prefix. Exactly so; the term "thio" is a prefix, like "per" or "di" or "ortho" or "tertiary" or "poly", etc. However, these are supposed to be substituents, which are moieties. A prefix is not a moiety; it is just a fragment of a name.
3. There still remains original point 14. Applicants have switched claim 34 to depend instead on claim 32, but that claim does not have "disease" in it either.
4. There still remains original point 15. The traverse is unpersuasive. Applicants point to the definitions provided for "alkylaminocarbonyl" etc, but that is not the term that the examiner is pointing to. It is not clear whether this in intended to cover e.g. phosphonic amides, as was stated previously.
5. There still remains original point 16. Norpinanyl needs to be removed as well.
6. There still remains original point 18. Applicants have misunderstood the basis of the rejection. The problem is not what is an alkoxyalkyl, but how the ranges operates. Does it apply to the first alkyl, or to both of the alkyls?
7. The "benzamidyl" on last line of page 65 is not a carbocycle, and indeed, it is not at all clear what it is. A carbocycle is a ring with just carbons present, period. It is not clear what this "benzamidyl" is, but it appears to have N present. It could be an amidine or an amide, to which a phenyl or a benzyl group is attached, or it could even be a benzimidazolyl group, which is not a carbocyclic group but is a heterocycle. Applicants need to draw what this group is, and explain why one of ordinary skill in the art would be able to figure out that this is what is intended. But please note that a group of the form X-Y-, where X is a carbocycle, and Y is some

linker, is not a carbocycle; it is a Y group substituted by a carbocycle. Deletion is suggested.

8. The second step is unclear in claim 19; it is not consistent with the preamble either. The claim is a method of inhibiting, but the last step is not an inhibition step, but "determining." Does determining mean measuring the inhibition after it has occurred? Or is it just the mental step of observing that the inhibition has occurred or what? For example, suppose that the cytokine inhibits all the cellular processes, i.e. the cell inside someone's body dies, and suppose that the observer does not notice that this one cell has died. The preamble seems to have been met; the activity was inhibited, but step (b) isn't met because the cell death is unnoticed. Would that fall within the claim or not?
9. The phrase "cellular process or activity" is unclear. What is the difference between process and activity? Isn't every activity a process and vice versa? Is applicant using some specialized meaning of "process" that is somehow different from "activity"?
10. Unsaturated hydrocarbons of one carbon are not possible, e.g. $C_{(1-20)}$alkenyl should be $C_{(2-20)}$alkenyl.
11. Similarly, $C_{(1-20)}$tetraaminoalkyl is impossible, since four aminos will require at least two carbons.
12. The scope of claims 23 and 24 is unclear. For most cytokines, so little is known that it is unclear which category, if any, the cytokine belong in. The public would be forced to unduly experiment to determine which category a given cytokine belonged in.

13. "Thioalkyl" is not standard nomenclature. Thio as a generic prefix simply indicating the presence of sulfur. It is of course possible that the term refers to HS-alkyl-, which is properly called the mercaptoalkyl group. It is also possible that it is intended to refer to the alkyl-S- group, which is properly called the alkylthio group. It could even possibly refer to the replacement of a carbon in an alkyl with a Sulfur, e.g. CH_3-S-CH_2- or possibly the sulfur could be a double bonded substituent rather than a single bonded one, e.g. CH_3-C(=S)-CH_2- This specification gives no clear evidence as to which of these plausible choices was originally intended, as the extensive list of definitions does not cover this.

Claims 1-7, 18-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. The third structural formula in claim 1 lacks description in the specification. This is a generic formula where R_4 is absent. No such formula exists in the specification, nor does the definition of R_4 include that option. Although there are a few such species present, that does not provide description for the genus itself.

B. The choices of R_2 and R_3 as haloalkyl and alkoxyalkyl lacks description in the specification. The definition of these variables on page 9, lines 3-8 does not include these particular choices. Applicants point to page 17 and 21, but that simply defines what these terms means; it does not state that R_2 and R_3 can be these choices. For example, the claim now covers a species with $R_2 = R_3$ = 5-iodopentyl. No such species exist in the specification nor is there any genus which embraces such species.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other choices, does not reasonably provide enablement for assorted haloalkyl and alkoxyalkyl choices, and in the last choice of methylphenyl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The definition of these variables on page 9, lines 3-8 does not include these particular choices. Since the teaching of how to use is tied to this definition, the specification fails to provide a teaching of how to use for such a compound. Thus, a compounds with $R_2 = R_3$ = methylphenyl has no teaching of how to use, as it does not fall within the specification formula to which utility is tied.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few substituent choices, e.g. amino and OH, does not reasonably provide enablement for nearly all the others. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The same reasons apply here as in the previous rejection. For example, the third claim 4 choice is COOH. None of the page 9, lines 3-8 choices have COOH as a substituent on the e.g. alkyl, etc. The same is true for furyl etc --- furyl is not a permitted substituent on anything.

Claims 10, 11, 14, 15, 17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for one isomer, does not reasonably provide enablement for the other isomer. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

These species are not embraced by the generic formula for reason set forth in point A above. Testing appears showing species to be active (thereby giving a utility), but the testing is done only on one isomer, not the other. Limitation to the tested isomer will resolve the matter.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to solvates. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." Hence, applicants must show that solvates can be made, or limit the claims accordingly.

With regard to *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, the Court held lack of enablement because the disclosed procedures in the specification did not even produce the claimed compounds. That is exactly the case here as well. There are a number of examples reported; not one of them produced a solvate.

Applicants state, "The formation of a solvate is within the skill of a person having ordinary skill in the art." One skilled in the art knows that solvates are prepared by exposing the compound to solvent (e.g. by preparing in the presence of solvent) and then isolating the solid. If the compound inherently forms solvates, then one will get a solvate; if not, one will not. That is, some compounds form solvates; some do not. These compounds, judging by the evidence of the specification, are in the latter category. The specification teaches no methods for overcoming this deficiency, i.e. to force a compound, which does not naturally form one, to form a solvate. The specification does not even seem to be aware of the problem. The remarks do not state how to do this, nor does the examiner know of any such technique. The reference is noted, but as the remarks state, it is directed to what a solvate is, not on how to force a compound to form a solvate if it does not naturally form one.

Claims 19-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the

issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444. The analysis is as follows:

(1) Breadth of claims:

a) Scope of method. The scope is colossal. It covers inhibiting any activity mediated by any cytokine, without further limitation (see page 20, lines 27-30). It thus probably covers most normal cellular processes and probably covers most diseases, and possibly virtually all diseases.

Cytokines are extraordinarily diverse in their structure and function. The term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment.

As for structure, most Cytokines are unrelated in terms of sequence.

Some attempts have been made to organize cytokines along lines of function, which show the tremendous variety of what is covered by "cytokine". For example, one category is chemokines, a generic name given to a family of pro-inflammatory activation-inducible Cytokines. These include a) SIS family such as SIS-alpha, SIS-gamma and SIS-epsilon, b) SIG family including JE, KC, MGSA (melanoma growth stimulatory activity), PF4 (platelet factor-4), PBP (platelet basic protein), LDCF (lymphocyte-derived chemotactic factor), RANTES, and SMC-CF, c) SCY family including SCY A1, SCY A2, SCY A3, SCY A4, SCY A5, SCY A6, SCY A7, SCY A8, SCY A9, SCY A10, SCY A11, SCY A12, SCYA13, SCY A14, SCY A15, SCY A16, SCY A17,

SCY A18, SCY A19, SCY A20, SCY A21, SCY A22, SCY A23, SCY A24, SCY A25, SCY A26 and many others as well.

Another category is Motogenic cytokines, a category Cytokines that influence the motility and migration of cells in ways other than affected by chemotactic processes. The collective term is an functional definition and there is no structural basis that would allow different factors to be classified as motogenic cytokines. Examples include AAMP (Angio-associated migratory cell protein), Adrenomedullin, AMF (autocrine motility factor), ATX (autotaxin), B16-F1 melanoma autocrine motility factor, DF (dissociation factor), Epitaxin, FDMF (fibroblast-derived motility factor), FMSF (fibroblast motility-stimulating factor) ISF (invasion stimulating factor), Ladsin, Monocyte-derived scattering factor, MSF (migration stimulating factor), PDMF (pancreatic cancer-derived motility factor), SF (scatter factor), SFL (scatter factor-like), and Vitronectin.

Another category is the B-cell growth factor (BCGF), which includes CD23, IL1, IL2, IL4, IL5, IL6, IFN-gamma, TNF-alpha and TNF-beta.

Another type are the colony stimulating factors, which regulate white blood cell production and orchestrate the control of the growth and differentiation of bone marrow progenitor cells. These include M-CSF (macrophage-specific), G-CSF (granulocyte-specific), GM-CSF (macrophage/granulocyte-specific), IL3 (multifunctional), IL-7 and Stem Cell Factor (SCF) and MEG-CSA (megakaryocyte-specific).

A large category of cytokines is the angiogenisis factors, which include aFGF, ANF, Angiogenin, Angiotropin, AtT20-ECGF, B61, bFGF, CAM-RF, ChDI, CLAF, ECGF, ECI, EDMF, EGF, EMAP, Neurothelin, Endostatin, Endothelial cell growth inhibitor, Endothelial cell-viability maintaining factor, Epo, FGF-5, IGF-2, HBNF, HGF, HUAF,

IFN-gamma, IL1, K-FGF, LIF, MD-ECI, MECIF, Oncostatin M, PD-ECGF, PDGF, PF4, PlGF, Prolactin, TNF-alpha, TNF-beta, Transferrin, VEGF, and others.

There are many, many other cytokines, including IL8, IL9, IL10, IL11, IL12, IL-13, IL-14, IP-10, GRO, and 9E3.

The claims then cover all activities of this extreme diverse group of proteins. Even for claim 25, that covers 19 different cytokines. For a number of these, e.g. the IL ones above 12, very little is known.

b) Scope of compounds employed. In addition, the scope of the compounds themselves is very large. There are four variables each with a substantial number of choices for what these variables can be. Moreover, many of these choices are themselves very broad, such as "heterocyclic". Claim 1 and claim 37 each cover billions of compounds.

(2) The nature of the invention and predictability in the art: The invention is directed toward the action of cytokines and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited value, except to make clear what a broad range of disorders is involved. Page 10-11 provides a immense list of disorders, including some very broad categories such as "Inflammatory diseases or disorders" (of which there are hundreds), and "autoimmune diseases" The dosage range

information is as broad as a million fold range (page 42 line 32) and is generic as to the particular disease. That is, it is not linked to any particular disorder.

(4) State of the Prior Art. So far as the examiner is aware, pyridopyrimidine triones have not been used as cytokine regulatory pharmaceuticals. In fact, the entire area of agents designed to regulate cytokines is extremely new, although it is quite possible that some medicines operate that way without that being understood at the time the medicine was first used. Almost all Cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most Cytokines have ubiquitous biological activities, their physiologic significance as normal regulators of physiology is often difficult to assess. The activities of cytokines as a group are extremely complex. Many Cytokines show stimulating or inhibitory activities and may synergize or antagonize also the actions of other factors. A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other Cytokines present at the same time, and even on the temporal sequence of several Cytokines acting on the same cell. The responses elicited by Cytokines are therefore

contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions.

(5) Working Examples: Example 12 and both examples 11 show that most (but not all) of the compounds tested suppress IL-4 or IL-12 signaling, or both. These are just a tiny portion of the cytokines embraced, and these examples do not demonstrate that these compounds have any *in vivo* properties, as these are *in vitro* tests.

(6) Skill of those in the art: The skill level in the art is low, relative to the complexity of task (see point 4 above). In general Cytokines act on a wider spectrum of target cells even than hormones and, unlike hormones, Cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function. Most cytokines are of unknown, or little known, function. There is no clear idea how many cytokines there are, as new ones are being discovered all the time. Except for a very few, regulation of the cytokines is a very poorly understood area.

(7) The quantity of experimentation needed: Extensive experimentation will be needed; see point 4. This is in part because of the vast scope and complexity of this area. More extensive experimentation than normal is needed because it is already established for at least one cytokine (α-TNF, one of the most extensively studied cytokines) that sometimes suppressing it makes matters worse when one would have expected better. That is, Tuberculosis and MS clearly have α-TNF involvement, but the α-TNF antagonist Remicade has been shown to make matters worse for these! Likewise, while α-TNF has a role in congestive heart failure, patients with CHF are now told to avoid using

Remicade because testing showed it to be worse than placebo. The amount of experimentation needed is greater in part because of the fact that it appears that in many cases, suppression of one cytokine simply means that another cytokine will take up the slack.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Objections

Claims 4-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. There is no provision in claim 37 for such substituents. For example, claim 4 lists carboxyl or heterocyclic, yet none of the claim 37 choices have carboxyl or heterocycle as a substituent for R_2 or R_3.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch

Primary Examiner

Art Unit 1624

May 29, 2002